neuronal activity in the locus cœruleus[5–7] and decreased noradrenaline release.[8,9] While clonidine and the opiates have similar effects on the locus cœruleus, clonidine appears to exert specific effects through non-opiate, alpha-2 adrenergic receptors.[6,7] These data suggested that the opiate-withdrawal syndrome is due to increased noradrenergic neuronal activity in areas such as the locus cœruleus which are regulated both by alpha-2 adrenergic and opiate receptors.

Our preliminary results in man support a noradrenergic system mediation of opiate withdrawal and suggest that clonidine may be a more definitive treatment for opiate withdrawal than others now available.

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HLA AND CONGENITAL ADRENAL HYPERPLASIA LINKAGE CONFIRMED

SIR,—Congenital adrenal hyperplasia (C.A.H.) is an autosomal recessive disease, associated in most cases with 21-hydroxylase deficiency.[1,2] Dupont et al.[3] suggested that the locus responsible for 21-hydroxylase deficiency is in close linkage with the HLA system. We have typed six families with one or more children with C.A.H. and report data supporting this linkage (table).

HLA typing was done by the standard two-stage National Institutes of Health lymphocytotoxicity test. 118 different sera were used to detect HLA A, B, and C antigens with the exception of CW6. In all families in which the segregation of W4 and W6 could be determined these antigens behaved as expected. In all families the segregation of the HLA haplotypes was established. Seven children with C.A.H. confirmed biochemically to be due to 21-hydroxylase deficiency were studied. The salt-losing form of 21-hydroxylase deficiency was present in four families while the remaining families (A and E) had the non-salt-losing form.

In family B both children had the HLA haplotype A3, BW47. The children seemed to be HLA homozygous although the parents were not first cousins and denied any known consanguinity. Family A was ascertained through child 5, a girl with C.A.H. The HLA typing of the family showed that her oldest brother was HLA identical. This 23-year-old man was further investigated and on both clinical and biochemical grounds was considered to be homozygous for 21-hydroxylase deficiency. Thus, the diagnosis was first suggested by HLA typing and then confirmed by clinical and biochemical studies (this case will be discussed in greater detail elsewhere). In a Pakistani family (F) the parents were first cousins and the only affected child was an HLA homozygote. In this family, child 4 carried a maternal HLA A/C,B recombinant haplotype while inheriting the same paternal haplotype as the affected sib. Thus, the two children (4 and 5) are HLA indentical at the A locus but different at the C, B loci showing that the gene for C.A.H. segregated with HLA-B rather than with HLA-A since child 4 "escaped" 21-hydroxylase deficiency. In three families (C, D, and E) with two children discordant for 21-hydroxylase deficiency the affected and unaffected children were not HLA identical.

In our families and those of Dupont et al.[3] no recombination between the HLA-B locus and the gene for C.A.H. has been found in a total of 35 children (or a total of 40 meiotic divisions including the family F first cousins). However, two recombinants between HLA A and B have been found in the twelve families. No association between particular HLA antigens and 21-hydroxylase deficiency gene occurred.

These findings have implications for both prenatal and postnatal diagnosis of 21-hydroxylase deficiency. Biochemical tests, though encouraging, have not yet provided unequivocal means of diagnosis in fetal life.[4] If diagnosis proves possible by the HLA typing of amniotic cells taken in the second trimester, it will allow parents with a previous previously affected child the opportunity to consider selective abortion. The ethics of abortion of a fetus with a condition amenable to postnatal treatment and compatible with life must be carefully considered. Unequivocal diagnosis in early pregnancy would make the more positive goal of prenatal treatment to prevent clitoral enlargement more feasible. HLA types of amniotic cells in late pregnancy or of cord-blood lymphocytes would supplement biochemical studies and allow early diagnosis and prompt treatment. Finally, identification of heterozygotes can be made with greater certainty thus facilitating the study of the carrier

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HLA GENOTYPES IN SIX FAMILIES WITH C.A.H.

Family	Parents	HLA haplotypes	Children: HLA haplotypes					
			1	2	3	4	5	6
A	F A2,B17/A1,B15,Cw3 M A10,B18/A9,B12	a/b c/d	a/c†	a/d	b/c	a/d	a/c*	b/c
B	F A3,Bw47/A2,B12 M A3,Bw47/A?.B7	a/b c/d	a/c*	a/c*				
C	F A11,Bw22,Cw3/A11,B27,Cw2 M A3,B40/A2,B17,Cw5	a/b c/d	a/c*	b/d				
D	F A2,Bw35,Cw4/A29,B–,Cw5 M A2,B12/A1,B8,Cw5	a/b c/d	a/c*	b/d				
E	F A10,B27,Cw1/A1,B8 M A3,B7/A9,B12,Cw4	a/b c/d	a/d	a/c*				
F	F A1,B5,/A10,B40 M A1,B5/A11,Bw35,Cw4	a/b c/d	b/d	b/d	b/c	a/cxd‡	a/c*	

* Affected child. † 21-hydroxylase deficiency homozygote, clinically normal (see text).
‡ HLA recombinant: HLA-A1,-B5/A1, Bw35,Cw4.
F = father; M = mother.

state and distinguishing the mildly affected homozygote in difficult cases.[5]

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SIR,—We can confirm that the gene for adrenogenital syndrome (21-hydroxylase deficiency type) is closely linked to HLA, as reported by Dupont et al.[1]

Three kindreds (A, B, and C) were ascertained through a female child with raised urinary 17-ketosteroids and virilising adrenogenital syndrome. Two of the propositi have affected brothers (raised urinary 17-ketosteroids); all five children have responded to corticosteroids. Genetic marker data on the individuals in family A have been reported previously as part of a study of a kindred with a chromosome abnormality.[2] The abnormality has lately been determined to be a translocation t(2;10) (q21;q24)[3] and is believed to be unrelated to adrenogenital syndrome. This family was HLA typed several years ago, with a limited range of HLA antisera. The results of typing the three kindreds for the closely linked chromosome 6 markers,[4] HLA-A, HLA-B, Bf (properdin factor B), and red cell glyoxalase are shown in table I.

A summary of lod scores[5] (logarithm of the odds) for linkage of the HLA-B, Bf region with adrenogenital syndrome is shown in table II. Dupont et al.[1] used e_1 corrections in the calculation of the scores in their families. We believe this is not appropriate in the calculation of lod scores for linkage of a recessive trait with a co-dominant, multiallelic marker such as HLA. Lod scores for the families of Dupont et al. have been recalculated directly from first principles, without corrections, and are presented in table I. The recalculated peak lod score is 4·6 instead of 3·4. Since HLA-B and Bf are very closely linked,[4] we have used information from both systems to determine the parental contribution of genes in this region of chromosome 6 in the three new families. Thus, the assignment of

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TABLE I—CHROMOSOME 6 HAPLOTYPES IN THREE FAMILIES WITH ADRENOGENITAL SYNDROME

Family	Parents					Children				
	Sex	GLO	Bf	HLA-B	HLA-A	Sex	GLO	Bf	HLA-B	HLA-A
A(10854)	M	1	S	–	2	M*	2	F	–	3
		2	F	–	3		2	S	7	2
	F	2	S	7	2	F	1	S	–	3 or 2
		2	S	–	3		2	S	7	2 or 3
						F	2	F	–	3
							2	S	–	3
						F*	2	F	–	3
							2	S	7	2
B(D151)	M	1	S	7	2	M	1	S	7	2
		2	F	–	26		1	S	12	32
	F	1	S	12	32	M*	2	F	–	26
		1	S	8	9		1	S	12	32
						F*	2	F	–	26
							1	S	12	32
C(D152)	M	1	S	7	3	F	1	S	7	3
		1	S	40	2		2	F	14	1
	F	2	F	14	1	F*	1	S	7	3
		2	S	14	–		2	S	14	–

*Adrenogenital syndrome. GLO=red-cell glyoxalase.

TABLE II—LOD SCORES FOR LINKAGE BETWEEN HLA-B (OR Bf) AND ADRENOGENITAL SYNDROME (21-HYDROXYLASE DEFICIENCY A.G.S.)

Kindred*	Type of A.G.S.	Chromosome 6 locus	Lod score for recombination fraction (θ) of:					
			0·00	0·01	0·02	0·03	0·04	0·05
1	Salt losing	HLA-B	0·602	0·585	0·567	0·550	0·533	0·515
2	Salt losing	HLA-B	0·602	0·585	0·567	0·550	0·533	0·515
3	Salt losing	HLA-B	0·602	0·585	0·567	0·550	0·533	0·515
4	Salt losing	HLA-B	0·727	0·705	0·684	0·662	0·640	0·618
5	Compensated	HLA-B	1·329	1·303	1·276	1·249	1·222	1·194
6	Salt losing	HLA-B	0·727	0·710	0·692	0·675	0·657	0·639
A	Salt losing	HLA-B, Bf	0·852	0·826	0·800	0·773	0·746	0·721
B	Compensated	HLA-B, Bf	0·727	0·705	0·684	0·662	0·640	0·618
C	Salt losing	HLA-B, Bf	0·288	0·268	0·249	0·231	0·214	0·198
Total	..	..	6·456	6·272	6·086	5·902	5·718	5·533

*Families 1–6 of Dupont et al.

adrenogenital syndrome to the HLA region is confirmed with a total peak lod score > 6 (odds of 10^6:1) at $\frac{1}{2} \sim 0{\cdot}00$.

Two additional conclusions may be drawn from these data. First there is no evidence that the genes for the salt-losing and compensated forms of adrenogenital syndrome have a different linkage distance to HLA-B. Second, Dupont et al. observed that adrenogenital syndrome is on the HLA-B side of HLA-A, basing the suggestion on a single family with an HLA-B: HLA-A recombinant. Child 2 in our family A is either a paternal Bf:HLA-A recombinant or a maternal HLA-B:HLA-A recombinant. In the former case the adrenogenital syndrome gene segregates with Bf, and in the latter the gene segregates with HLA-B, confirming, in either event, that the gene for the adrenogenital syndrome is on the HLA-B side of HLA-A.

There is no evidence for association of the gene(s) for adrenogenital syndrome with a specific HLA-B allele in the nine reported families; thus, the HLA-B and adrenogenital-syndrome loci are apparently far enough apart for linkage disequilibrium not to be prominent. The adrenogenital syndrome locus (loci) may lie as much as a few centimorgans from HLA-B. More precise mapping will be possible when red-cell-glyoxalase: HLA recombinants are found in families with the adrenogenital syndrome.

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PRENATAL DIAGNOSIS OF PRIMARY PITUITARY DYSGENESIS

SIR,—Primary pituitary dysgenesis is a rare inherited disease in which where we may find hypoglycæmia, respiratory distress, small sella turcica, hypothyroidism, adrenal insufficiency, and ectopic testes.[1,2]

We have attempted prenatal diagnosis in two pregnancies at risk for primary pituitary dysgenesis. These were the 5th and 6th pregnancies. The results of the 1st and the 4th were normal girls. The other two gave affected boys.[1,2] The parents are cousins.

Prolactin activity was measured in amniotic fluid obtained at 16 weeks' gestation. Amniotic fluid was frozen until analysed. Prolactin activity was measured in 20 amniotic fluids from controls at the same gestational age. Prolactin was measured by double-antibody radioimmunoassay.[3] Prolactin levels were low (355 ng/ml) in the 5th pregnancy. The parents wanted to continue the pregnancy; the result was an affected boy. In the 6th pregnancy prolactin levels were normal (1500 ng/ml).

Clements et al.[4] found that prolactin levels in amniotic fluid averaged 1314 ng/ml (range 270–2950) at 15–17 weeks. None of our controls had a prolactin level at 16 weeks fetal age under 1337 ng/ml (range 1337–2487).

The 6th pregnancy was continued and a normal girl was born. She is now 6 months old, and hormone studies, X-rays of the sella turcica, and bone age are normal. Serum-prolactin was measured at 2 days of age and found to be 202 ng/ml (term cord-blood values averaged 199 ng/ml).

Prenatal diagnosis of primary pituitary dysgenesis early enough to give the parents of an affected fetus the choice of termination of pregnancy now seems possible.

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CIMETIDINE MAINTENANCE: HOW LONG?

SIR,—Dr Blackwood and colleagues (March 25, p. 626) found that nearly all duodenal ulcers which had been healed by an initial course of cimetidine relapsed if not further treated (21 out of 24 placebo-treated patients had recurrent duodenal ulcers within six months of initial healing) while only 5 out of 21 patients had ulcer recurrences during a six-month period of treatment with bedtime cimetidine. Blackwood et al. conclude that bedtime cimetidine prevents relapse of duodenal ulcers.

Almost identical suppression of the tendency of duodenal ulcers to relapse has been noted with two different cimetidine maintenance regimens studied in unpublished trials done in Nottingham (and Lincoln) and Dundee. In Nottingham twice daily cimetidine (400 mg morning and night) resulted in a relapse-rate of only 25% after six months; 75% of ulcers which had healed after an initial course of cimetidine, relapsed within six months during treatment with placebo. In Dundee 98 patients were maintained in full doses of cimetidine (200 mg three times daily after food and 400 mg at night) for three to twelve months after primary healing of the duodenal ulcers. The recurrence-rate was 19%. Thus cimetidine not only heals most duodenal ulcers but also it usually prevents relapse of healed ulcers when treatment with the drug is continued for six to twelve months.

Unfortunately Blackwood et al. do not say what happened to their patients after maintenance treatment with cimetidine was stopped. In Nottingham a further 40% of the cimetidine-treated patients relapsed during eight months after cessation of maintenance treatment, raising the rate of recurrence to about 70%. In Dundee follow-up for nearly two years after the end of maintenance treatment revealed relapse in a further 44%, giving a rate of relapse during and after treatment of 63%. It is not clear whether these overall relapse-rates differ significantly from the rate of relapse of placebo-treated patients, so we still do not know how long we need to treat patients with cimetidine before we can be sure that we are not merely deferring their visit to the surgeon.

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HB_s Ag IN SUPERFICIAL ARTERY OF PATIENT WITH POLYMYALGIA RHEUMATICA

SIR,—Liver enzyme and other functional abnormalities in polymyalgia rheumatica are well known. Corticosteroid therapy rapidly reverses these anomalies.[1,2] Liver biopsy usually reveals normal parenchyma or fatty degeneration,[1,3] but in one case granulomatous hepatitis associated with fatty degeneration and thickening of the walls of small intrahepatic arteries has been reported.[4]

Hepatitis B antigen (HB_sAg) has never been found in cases

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